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991 F.2d 781, \*; 1993 U.S. App. LEXIS 8603, \*\*;  
26 U.S.P.Q.2D (BNA) 1529; 93 Daily Journal DAR 5248

IN RE GRAEME I. BELL, LESLIE B. RALL and JAMES P. MERRYWEATHER

92-1375

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

991 F.2d 781; 1993 U.S. App. LEXIS 8603; 26 U.S.P.Q.2D (BNA) 1529; 93 Daily Journal DAR 5248

April 20, 1993, Decided

**PRIOR HISTORY:** [\*\*1] Appealed from: U.S. Patent and Trademark Office, Board of Patent Appeals & Interferences. Serial No. 07/065,673.

**DISPOSITION:** REVERSED

#### CASE SUMMARY

**PROCEDURAL POSTURE:** Appeal from a decision of the U.S. Patent and Trademark Office Board of Patent Appeals and Interferences, which affirmed an examiner's final rejection of appellants' application as unpatentable on the ground of obviousness under 35 U.S.C.S. § 103 (1988).

**OVERVIEW:** Appellants filed a patent application with the U.S. Patent and Trademark Office (PTO). The application's claims were directed to nucleic acid molecules containing human sequences, which code human insulin-like growth factors. An examiner rejected appellants' application on the ground of obviousness under 35 U.S.C.S. § 103 (1988). The Board of Patent Appeals and Interferences affirmed the decision of the examiner. On appeal, the court reversed, reasoning the PTO did not show how the prior art references, either alone or in combination, taught or suggested the claimed invention, and thus, that it failed to establish a prima facie case of obviousness. The appellate court further determined that given the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities was the human sequence, the claimed sequences would not have been obvious under § 103.

**OUTCOME:** Decision of the board reversed, because the board erred in concluding that the claimed nucleic acid molecules would have been obvious in light of the cited prior art.


**CORE TERMS:** sequence, amino acid, gene, protein, codon, nucleic acid, teaching, obviousness, teach, amino acids, examiner, probe, genetic code, nucleotide, invention, molecules, coded, prima facie case, prima facie, composition, burden of establishing, cloning, patent, corresponding, correspondent, advantageous, degeneracy, affirming, isolating, nucleic


**CORE CONCEPTS** - ♦ [Hide Concepts](#)

 [Patent Law > Nonobviousness > Tests & Proof of Obviousness](#)  
 [Patent Law > U.S. Patent & Trademark Office Prosecution Procedures > Interferences](#)  
 [Patent Law > Jurisdiction & Review > Standards of Review](#)

EXHIBIT


✚ The appellate court reviews an obviousness determination by the U.S. Patent and Trademark Office Board of Patent Appeals and Interferences de novo.


 [Evidence > Procedural Considerations > Burdens of Proof, Presumptions & Inferences](#)

 [Patent Law > Nonobviousness > Tests & Proof of Obviousness](#)


 [Patent Law > U.S. Patent & Trademark Office Prosecution Procedures > Interferences](#)


✚ The U.S. Patent and Trademark Office Board of Patent Appeals and Interferences bears the burden of establishing a case of prima facie obviousness.

 [Evidence > Procedural Considerations > Burdens of Proof, Presumptions & Inferences](#)


 [Patent Law > Nonobviousness > Tests & Proof of Obviousness](#)


✚ A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art.

 [Evidence > Procedural Considerations > Burdens of Proof, Presumptions & Inferences](#)


 [Patent Law > Nonobviousness > Tests & Proof of Obviousness](#)

✚ Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination.

 [Patent Law > Nonobviousness > Tests & Proof of Obviousness](#)

 [Patent Law > Jurisdiction & Review > Standards of Review](#)

✚ What a reference teaches and whether it teaches toward or away from the claimed invention are questions of fact.

 [Patent Law > Patentable Subject Matter > Products](#)

✚ The patentability of a product does not depend on its method of production.

**COUNSEL:** Robert P. Blackburn, Chiron Corporation, of Emeryville, California, argued for appellant. With him on the brief were Debra A. Shetka and Thomas E. Ciotti, Morrison & Foerster, of Palo Alto, California, and Donald S. Chisum, Morrison & Foerster, of Seattle, Washington.

Teddy S. Gron, Associate Solicitor, Office of the Solicitor, of Arlington, Virginia, argued for appellee. With him on the brief was Fred E. McKelvey, Solicitor. Of counsel were John W. Dewhirst, Lee E. Barrett, Richard E. Schafer and Albin F. Drost.

**JUDGES:** Before RICH, LOURIE, and SCHALL, Circuit Judges.

**OPINIONBY:** LOURIE

**OPINION:**

[\*782] LOURIE, Circuit Judge.

Applicants Graeme I. Bell, Leslie B. Rall, and James P. Merryweather (Bell) appeal from the March 10, 1992 decision of the U.S. Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences, Appeal No. 91-1124, affirming the examiner's final rejection of claims 25-46 of application Serial No. 065,673, entitled "Preproinsulin-Like Growth Factors I and II," as unpatentable on the ground of obviousness under 35 U.S.C. § 103 (1988). Because the Board **[\*\*2]** erred in concluding that the claimed nucleic acid molecules would have been obvious in light of the cited prior art, we reverse.

## BACKGROUND

The claims of the application at issue are directed to nucleic acid molecules (DNA and RNA) n1 containing human sequences n2 which code for human insulin-like growth factors I and II (IGF), single chain serum proteins that play a role in the mediation of somatic cell growth following the administration of growth hormones. n3

-----Footnotes-----

n1 A basic familiarity with recombinant DNA technology is presumed. For a general discussion, see In re O'Farrell, 853 F.2d 894, 895-99, 7 USPQ2d 1673, 1674-77 (Fed. Cir. 1988).

n2 Interchangeably referred to as "native" sequences and "genes."

n3 Claim 25 is conceded to be representative of the claims at issue:

A composition comprising nucleic acid molecules containing a human sequence encoding insulin-like growth factor (hIGF) substantially free of nucleic acid molecules not containing said hIGF sequence, wherein said hIGF sequence is selected from the group consisting of:

(a) 5'-GGA CCG GAG ACG CUC UGC GGG GCU GAG CUG GUG GAU GCU CUU CAG UUC GUG UGU GGA GAC AGG GGC UUU UAU UUC AAC AAG CCC ACA GGG UAU GGC UCC AGC AGU CGG AGG GCG CCU CAG ACA GGU AUC GUG GAU GAG UGC UGC UUC CGG AGC UGU GAU CUA AGG AGG CUG GAG AUG UAU UGC GCA CCC CUC AAG CCU GCC AAG UCA GCU-3', wherein U can also be T;

(b) 5'-GCU UAC CGC CCC AGU GAG ACC CUG UGC GGC GGG GAG CUG GUG GAC ACC CUC CAG UUC GUC UGU GGG GAC CGC GGC UUC UAC UUC AGC AGG CCC GCA AGC CGU GUG AGC CGU CGC AGC CGU GGC AUC GUU GAG GAG UGC UGU UUC CGC AGC UGU GAC CUG GCC CUC CUG GAG ACG UAC UGU GCU ACC CCC GCC AAG UCC GAG-3', wherein U can also be T;

(c) nucleic acid sequences complementary to (a) or (b); and

(d) fragments of (a), (b) or (c) that are at least 18 bases in length and which will selectively hybridize to human genomic DNA encoding hIGF.

The other rejected claims are apparently directed to cellular hosts transformed with the claimed nucleic acid sequences. Because their fate is dependent upon that of claim 25, neither appellant nor the Patent and Trademark Office have considered them separately and we will not do so either.

-----End Footnotes----- **[\*3]**

**[\*783]** The relevant prior art consists of two publications by Rinderknecht n4 disclosing amino acid sequences for IGF-I and -II and U.S. Patent 4,394,443 to Weissman et al., entitled "Method for Cloning Genes." Weissman describes a general method for isolating a gene for which at least a short amino acid sequence of the encoded protein is known. The method involves preparing a nucleotide probe corresponding to the known amino acid sequence and using that probe to isolate the gene of interest. It teaches that it is advantageous to design a probe based on amino acids specified by unique codons. n5 The Weissman patent specifically describes the isolation of a gene which codes for human

histocompatibility antigen, a protein unrelated to IGF. It describes the design of the probe employed, stating that it was based on amino acids specified by unique codons.

-----Footnotes-----

n4 Rinderknecht et al., The Amino Acid Sequence of Human Insulin-like Growth Factor I and Its Structural Homology with Proinsulin, 253 The Journal of Biological Chemistry 2769-76 (1978); Rinderknecht et al., Primary Structure of Human Insulin-like Growth Factor II, 89 FEB Letters 283-86 (May 1978). **[\*\*4]**

n5 A sequence of three nucleotides, called a codon, codes for each of the twenty natural amino acids. Since there are twenty amino acids and sixty-four possible codons, most amino acids are specified by more than one codon. This is referred to as "degeneracy" in the genetic code. The term "unique" refers to an amino acid coded for by a single codon. See Amgen Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1207-08 n.4, 18 USPQ2d 1016, 1022 n.4 (Fed. Cir.), cert. denied, 116 L. Ed. 2d 132, 112 S. Ct. 169 (1991).

-----End Footnotes-----

The examiner rejected the claims as obvious over the combined teachings of Rinderknecht and Weissman. She determined that it would have been obvious, "albeit tedious," from the teachings of Weissman to prepare probes based on the Rinderknecht amino acid sequences to obtain the claimed nucleic acid molecules. According to the examiner, "it is clear from [Weissman] that the ordinary artisan knows how to find the nucleic acid when the amino acid sequence is known" and that "the claimed sequences and hosts would have been readily **[\*\*5]** determinable by and obvious to those of ordinary skill in the art at the time the invention was made."

The Board affirmed the examiner's rejection, holding that the examiner had established a prima facie case of obviousness for the claimed sequences "despite the lack of conventional indicia of obviousness, e.g., structural similarity between the DNA which codes for IGF-I and the amino acid sequence of the polypeptide which constitutes [sic] IGF-I." Slip op. at 6. The Board reasoned that "although a protein and its DNA are not structurally similar, they are correspondently linked via the genetic code." Id. at 4 n.1. In view of Weissman, the Board concluded that there was no evidence "that one skilled in the art, knowing the amino acid sequences of the desired proteins, would not have been able to predictably clone the desired DNA sequences without undue experimentation." Id. at 8.

The issue before us is whether the Board correctly determined that the amino acid sequence of a protein in conjunction with a reference indicating a general method of cloning renders the gene prima facie obvious.

## DISCUSSION

✦ We review an obviousness determination by the Board de novo. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). **[\*\*6]** Bell argues that the PTO has not shown how the prior art references, either alone or in combination, teach or suggest the claimed invention, and thus that it has failed to establish a prima facie case of obviousness.

We agree. ✦ The PTO bears the burden of establishing a case of prima facie obviousness. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). "A ✧ prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art." In re Rinehart, 531 F.2d 1048, 1051, 189 USPQ 143, 147 (CCPA 1976).

The Board supported the examiner's view that the "correspondent link" between **[\*784]** a

gene and its encoded protein via the genetic code renders the gene obvious when the amino acid sequence is known. In effect, this amounts to a rejection based on the Rinderknecht references alone. Implicit in that conclusion is the proposition that, just as closely related homologs, analogs, and isomers in chemistry may create a prima facie case, see *In re Dillon*, 919 F.2d 688, 696, 16 USPQ2d 1897, 1904 (Fed. Cir. 1990) **[\*\*7]** (in banc), cert. denied, 114 L. Ed. 2d 77, 111 S. Ct. 1682 (1991), the established relationship in the genetic code between a nucleic acid and the protein it encodes also makes a gene prima facie obvious over its correspondent protein.

We do not accept this proposition. It may be true that, knowing the structure of the protein, one can use the genetic code to hypothesize possible structures for the corresponding gene and that one thus has the potential for obtaining that gene. However, because of the degeneracy of the genetic code, there are a vast number of nucleotide sequences that might code for a specific protein. In the case of IGF, Bell has argued without contradiction that the Rinderknecht amino acid sequences could be coded for by more than  $10^{36}$  different nucleotide sequences, only a few of which are the human sequences that Bell now claims. Therefore, given the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities is the human sequence, the claimed sequences would not have been obvious.

Bell does not claim all of the nucleic acids that might potentially **[\*\*8]** code for IGF. Neither does Bell claim all nucleic acids coding for a protein having the biological activity of IGF. Rather, Bell claims only the human nucleic acid sequences coding for IGF. Absent anything in the cited prior art suggesting which of the possible sequences suggested by Rinderknecht corresponds to the IGF gene, the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences.

This is not to say that a gene is never rendered obvious when the amino acid sequence of its coded protein is known. Bell concedes that in a case in which a known amino acid sequence is specified exclusively by unique codons, the gene might have been obvious. Such a case is not before us. Here, where Rinderknecht suggests a vast number of possible nucleic acid sequences, we conclude that the claimed human sequences would not have been obvious.

-----Footnotes-----

<sup>n6</sup> We also express no opinion concerning the reverse proposition, that knowledge of the structure of a DNA, e.g., a cDNA, might make a coded protein obvious.

-----End Footnotes----- **[\*\*9]**

Combining Rinderknecht with Weissman does not fill the gap. "Obviousness" cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." *In re Fine*, 837 F.2d at 1075, 5 USPQ2d at 1598 (citing *ACS Hosp. Sys. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)). "What a reference teaches and whether it teaches toward or away from the claimed invention are questions of fact. See *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960-61, 220 USPQ 592, 599-600 (Fed. Cir. 1983), cert. denied, 469 U.S. 835, 83 L. Ed. 2d 69, 105 S. Ct. 127 (1984).

While Weissman discloses a general method for isolating genes, he appears to teach away from the claimed invention by emphasizing the importance of unique codons for the amino acids. Weissman suggests that it is generally advantageous to design a probe based on an amino acid sequence specified by unique codons, and also teaches that it is "counterproductive" to use a primer having more than **[\*\*10]** 14-16 nucleotides unless the known amino acid sequence has 4-5 amino acids coded for by unique codons. Bell, in contrast, used a probe having 23 nucleotides based on a sequence of eight amino acids, none

of which were unique. Weissman therefore tends to teach away from the claimed sequences since Rinderknecht shows that IGF-I has only a single amino acid with a unique codon and IGF-II has none.

**[\*785]** The PTO, in urging us to affirm the Board, points to the suggestion in Weissman that the disclosed method can "easily" be applied to isolate genes for an array of proteins including peptide hormones. The PTO thus argues that in view of Weissman, a gene is rendered obvious once the amino acid sequence of its translated protein is known. We decline to afford that broad a scope to the teachings of Weissman. While "a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests," In re Burckel, 592 F.2d 1175, 1179, 201 USPQ 67, 70 (CCPA 1979), we cannot say that Weissman "fairly suggests" that its teachings should be combined with those of Rinderknecht, since it nowhere suggests how to apply its teachings **[\*\*11]** to amino acid sequences without unique codons.

We conclude that the Board clearly erred in determining that Weissman teaches toward, rather than away from, the claimed sequences. Therefore, the requisite teaching or suggestion to combine the teachings of the cited prior art references is absent, see In re Fine, 837 F.2d at 1075, 5 USPQ2d at 1599, and the PTO has not established that the claimed sequences would have been obvious over the combination of Rinderknecht and Weissman.

Finally, the PTO emphasizes the similarities between the method by which Bell made the claimed sequences and the method taught by Weissman. The PTO's focus on Bell's method is misplaced. Bell does not claim a method. Bell claims compositions, and the issue is the obviousness of the claimed compositions, not of the method by which they are made. See In re Thorpe, 777 F.2d 695, 697, 227 USPQ 964, 966 (Fed. Cir. 1985) ("The patentability of a product does not depend on its method of production.").

#### CONCLUSION

Because we conclude that the combination of prior art references does not render the claimed invention obvious, **[\*\*12]** we reverse the Board's decision affirming the examiner's rejection of claims 25-46.

#### REVERSED

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Citation: 26 USPQ2d 1529

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Date/Time: Sunday, September 29, 2002 - 10:46 AM EDT

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